Enaminen van 3-ketotetrahydrothiofenen; bereiding en reacties

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SUMMARY

This thesis deals with the synthesis and some reactions of enamines derived from 3-ketotetrahydrothiophenes.

Although much work has been done in the field of enamine chemistry, enamines of heterocyclic ketones have been prepared only recently. One of these is the pyrrolidine enamine of 3-ketotetrahydrofuran (see Brannock *et al.*, 1963). Only one of the two possible bond isomers was isolated, namely 3-pyrrolidino-2,5-dihydrofuran.

In view of this it was of interest to examine the formation of enamines from 3-ketotetrahydrothiophenes, ketones which are also of importance in other investigations in this laboratory. Furthermore, since the enamines derived from these ketones are 3-*tert*-aminodihydrothiophenes, they might serve as precursors in the synthesis of new thiophene and tetrahydrothiophene derivatives. This supposition proved to be correct.

The novelty of synthesizing thiophenes and tetrahydrothiophenes *via* dihydrothiophenes is pointed out in a brief summary in chapter 1.

Chapter 2 describes the synthesis and properties of 3-ketotetrahydrothiophene and substituted 3-ketotetrahydrothiophenes. Some of these ketones were obtained by improved methods.

In chapter 3 the reaction of the ketones with different secondary amines is described. 3-Ketotetrahydrothiophene itself yielded an enamine-mixture which was found to consist of the 2,5- and the 4,5-dihydro isomer, the former dominating. Efforts to separate or isomerise these mixtures were not successful. Representatives of each type of enamine were obtained by use of appropriately substituted ketones. In addition the direct preparation of an immonium salt and also the reaction of 3-ketotetrahydrothiophene with cyclohexylamine are described.

By dehydrogenation of the unsubstituted 3-*tert*-aminodihydrothiophenes, using di-isopentyl disulfide as dehydrogenating agent, the corresponding 3-*tert*-aminothiophenes were obtained (chapter 4). Simple 3-*tert*-aminothiophenes were previously unknown. Their relative stability could support the opinion that the primary and

secondary aminothiophenes decompose through an unstable imino form (compare Gronowitz, 1963), as such a tautomer is impossible in the case of the tertiary aminothiophenes. Nevertheless the recently described 3-dimethylaminothiophene is reported to be very unstable to air (Sullivan and McCarthy, 1965).

Two methyl substituted 3-*tert*-aminothiophenes were prepared from the appropriate enamines. The spectra and pKa values of the different tertiary aminothiophenes are discussed.

Some electrophilic substitution reactions of 3-piperidinothiophene were examined, *i.e.* benzoylation, azo-coupling and nitrosation. The strong activation of the 2-position was clearly demonstrated by the successful reaction with benzoyl chloride in the presence of triethylamine. This behaviour is similar to that of ordinary enamines in acylation (see Stork *et al.*, 1963).

Unsuccessful attempts to prepare 2-*tert*-aminothiophenes are also mentioned in this chapter.

In chapter 5 reactions of the enamines which lead to tetrahydrothiophene derivatives are presented. By reduction with formic acid 3-*tert*-aminotetrahydrothiophenes were obtained. Their methiodides were prepared for physiological testing; a pronounced toxicity was found.

Reaction of the enamines with methanesulfonylchloride and triethylamine yielded the crystalline sulfene cycloadducts. The assigned structures of these adducts were supported by their protonmagnetic resonance spectra.

No Diels-Alder adducts could be obtained from our enamines and different dienes.

In conclusion a nucleophilic substitution reaction of the immonium salt prepared in chapter 3 is given.